

CM We claim:

1. A compound of the formula PS

71 (pyro)Glu-His-V-Ser-W-X-Y-Arg-Pro-Z TM (L)A

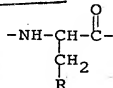
(I)

PS and the pharmaceutically acceptable salts thereof wherein:

P₁ V is tryptophyl, phenylalanyl or 3-(1-naphthyl)-L-alanyl;

P₁ W is tyrosyl, phenylalanyl or 3-(1-pentafluorophenyl)-L-alanyl;

P₁ X is a D-amino acid ^{residue}



704906
P₁ wherein R is

P₂ (a) a carbocyclic aryl-containing radical selected from the group consisting of naphthyl, anthryl, fluorenyl, phenanthryl, biphenyl, benzhydryl and phenyl substituted with three or more straight chain lower alkyl groups; or

P₂ (b) a saturated carbocyclic radical selected from the group consisting of cyclohexyl substituted with three or more straight chain lower alkyl groups, perhydronaphthyl, perhydrobiphenyl, perhydro-2,2-diphenylmethyl and adamantyl;

P₁ Y is leucyl, isoleucyl, nor-leucyl or N-methyl-leucyl;

P₁ Z is glycineamide or NH-R^1 , wherein

R^1 is lower alkyl, cycloalkyl, fluoro lower alkyl or
-NH-C(=O)-NH- R^2 wherein

~~tyrosyl~~

R^2 is hydrogen or lower alkyl.

2. The compound of Claim 1 wherein V is
tryptophyl or phenylalanyl; W is tyrosyl; X is
3-(2-naphthyl)-D-alanyl or 3-(2,4,6-trimethylphenyl)-D-
alanyl; Y is leucyl or N-methyl-leucyl; and Z is glycine
amide or ~~polyethylamide~~ ^{NHET}.

3. The compound of Claim 2 wherein X is
3-(2-naphthyl)-D-alanyl.

4. The compound of Claim 2 which is (pyro)Glu-
His-Trp-Ser-Tyr-3-(2-naphthyl)-D-alanyl-Leu-Arg-Pro-
Gly-NH₂ and the pharmaceutically acceptable acid salts
thereof.

5. The compound of Claim 3 which is (pyro)Glu-
His-Trp-Ser-Tyr-3-(2-naphthyl)-D-alanyl-N-methyl-Leu-Arg-
Pro-Gly-NH₂ and the pharmaceutically acceptable salts
thereof.

6. The compound of Claim 3 which is (pyro)Glu-His-
Trp-Ser-Tyr-3-(2-naphthyl)-D-alanyl-Leu-Arg-Pro-NHET and
the pharmaceutically acceptable salts thereof.

7. The compound of Claim 3 which is (pyro)Glu-His-
Trp-Ser-Tyr-3-(2-naphthyl)-D-alanyl-N-methyl-Leu-Arg-Pro-
NHET and the pharmaceutically acceptable salts thereof.

8. The compound of Claim 3 which is (pyro)Glu-His~~2~~
Phe-Ser-Syr-3-(2-naphthyl)-D-alanyl-Leu-Arg-Pro-Gly-NH₂
and the pharmaceuticly acceptable salts thereof.

5 9. The compound of Claim 2 wherein X is 3-(2,4,6-
trimethylphenyl)-D-alanyl.

10 10. The compound of Claim 9 which is (pyro)Glu~~2~~
His-Trp-Ser-Tyr-3-(2,4,6-trimethylphenyl)-D-alanyl-Leu~~2~~
Arg-Pro-Gly-NH₂ and the pharmaceutically acceptable salts
thereof.

15 11. A method of inhibiting ovulation in a female
mammalian subject which method comprises administering to
said subject an effective amount of a compound of the
formula PS

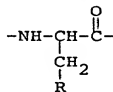
20 T (pyro)Glu-His-V-Ser-W-X-Y-Arg-Pro-Z TM (I) PS

PS or a pharmaceutically acceptable salt thereof wherein:

P V is tryptophyl, phenylalanyl or 3-(1-naphthyl)-L-
alanyl;

25 P W is tyrosyl, phenylalanyl or 3-(1-pentafluoro-
phenyl)-L-alanyl;

a P X is a D-amino acid residue



70520X

(P.F.T.) wherein R is

5 (a) a carbocyclic aryl-containing radical selected from the group consisting of naphthyl, anthryl, fluorenyl, phenanthryl, biphenyl, benzhydryl and phenyl substituted with three or more straight chain lower alkyl groups; or

10 (b) a saturated carbocyclic radical selected from the group consisting of cyclohexyl substituted with three or more straight chain lower alkyl groups, perhydro-naphthyl perhydrobiphenyl, perhydro-2,2-diphenylmethyl and adamantyl;

15 (c) Y is leucyl, isoleucyl, nor-leucyl or N-methyl-leucyl;

(d) Z is glycnamide or $\frac{1}{m}\text{NH}-\frac{1}{m}\text{R}^1$, wherein

(e) R^1 is lower alkyl, cycloalkyl, fluoro lower alkyl or

705201 $\text{-NH}-\overset{\text{O}}{\parallel}\text{C}-\text{NH}-\text{R}^2$ wherein

20 (f) R^2 is hydrogen or lower alkyl, or a pharmaceutical composition containing same.

a 12. A pharmaceutical composition ~~for inhibition of~~ ^{of an effective amount of} ~~ovulation in a female mammal~~ comprising a compound of the
25 formula (I)

71 (pyro)Glu-His-V-Ser-W-X-Y-Arg-Pro-Z TM (I) P3

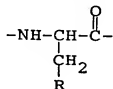
(I)

P₅ or a pharmaceutically acceptable salt thereof wherein:

P₁ V is tryptophyl, phenylalanyl or 3-(1-naphthyl)-L-alanyl;

P₁ W is tyrosyl, phenylalanyl or 3-(1-pentafluorophenyl)-L-alanyl;

P₁ X is a D-amino acid ^{residue}



~~70530 X~~

(P₁) where R is

P₂ (a) a carbocyclic aryl-containing radical selected from the group consisting of naphthyl, anthryl, fluorenyl, phenanthryl, biphenyl, benzhydryl and phenyl substituted with three or more straight chain lower alkyl groups; or

P₂ (b) a saturated carbocyclic radical selected from the group consisting of cyclohexyl substituted with three or more straight chain lower alkyl groups, perhydro-naphthyl, perhydrobiphenyl, perhydro-2,2-diphenylmethyl and adamantyl;

P₁ Y is leucyl, isoleucyl, nor-leucyl or N-methyl-leucyl;

P₁ Z is glycine or $\text{NH}-\text{R}^1$, wherein

~~70530~~ R^1 is lower alkyl, cycloalkyl, fluoro lower alkyl or

$\text{NH}-\text{C}(=\text{O})-\text{NH}-\text{R}^2$ wherein

P₁ R² is hydrogen or lower alkyl, in admixture with a pharmaceutically acceptable non-toxic carrier.

13. A method of treating endometriosis in a female mammalian subject which method comprises administering to

said subject an effective amount of a compound of the formula P_2

71 (pyro)Glu-His-V-Ser-W-X-Y-Arg-Pro-Z TM (I) R

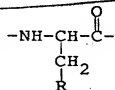
(I)

P_2 or a pharmaceutically acceptable salt thereof wherein:

P_1 V is tryptophyl, phenylalanyl or 3-(1-naphthyl)-L-alanyl;

P_1 W is tyrosyl, phenylalanyl or 3-(1-pentafluoro-phenyl)-L-alanyl;

P_1 X is a D-amino acid ^{residue}



T05409
(P_1+10) wherein R is

P_2 (a) a carbocyclic aryl-containing radical selected from the group consisting of naphthyl, anthryl, fluorenyl, phenanthryl, biphenyl, benzhydryl and phenyl substituted with three or more straight chain lower alkyl groups; or

P_2 (b) a saturated carbocyclic radical selected from the group consisting of cyclohexyl substituted with three or more straight chain lower alkyl groups, perhydro-naphthyl, perhydrobiphenyl, perhydro-2,2-diphenylmethyl and adamantyl;

P_1 Y is leucyl, isoleucyl, nor-leucyl or N-methyl-

leucyl;

F_1 Z is glycine or NH-R^1 , wherein

F_1 R^1 is lower alkyl, cycloalkyl, fluoro lower alkyl or

NH-C(=O)-NH-R^2 wherein

F_1 R^2 is hydrogen or lower alkyl, or a pharmaceutical

composition containing same.

14. A pharmaceutical composition for treatment of
endometriosis in a female mammal comprising a compound of
the formula

(pyro)Glu-His-V-Ser-W-X-Y-Arg-Pro-Z

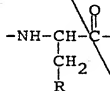
(I)

or a pharmaceutically acceptable salt thereof wherein:

V is tryptophyl, phenylalanyl or 3-(1-naphthyl)-L-alanyl;

W is tyrosyl, phenylalanyl or 3-(1-pentafluorophenyl)-L-alanyl;

X is a D-amino acid



wherein R is

(a) a carbocyclic aryl-containing radical selected
from the group consisting of naphthyl, anthryl,
fluorenyl, phenanthryl, biphenyl, benzhydryl and phenyl
substituted with three or more straight chain lower alkyl

groups; or

(b) a saturated carbocyclic radical selected from the group consisting of cyclonexyl substituted with three or more straight chain lower alkyl groups, perhydronaphthyl, perhydrobiphenyl, perhydro-2,2-diphenylmethyl and adamantyl;

Y is leucyl, isoleucyl, nor-leucyl or N-methyl-leucyl;

Z is glycinamide or -NH-R^1 , wherein

R^1 is lower alkyl, cycloalkyl, fluoro lower alkyl or -NH-C(=O)-NH-R^2 wherein

R^2 is hydrogen or lower alkyl, in addition with a pharmaceutically acceptable, non-toxic carrier.

14.
15. A method of treating benign prostatic hypertrophy in a male mammalian subject which method comprises administering to said subject an effective amount of a compound of the formula

20 Tl (pyro)Glu-His-V-Ser-W-X-Y-Arg-Pro-Z TM (I) PS

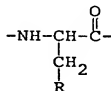
(I)

PS or a pharmaceutically acceptable salt thereof wherein:

25 R_1 V is tryptophyl, phenylalanyl or 3-(1-naphthyl)-L-alanyl;

R_1 W is tyrosyl, phenylalanyl or 3-(1-pentafluorophenyl)-L-alanyl;

a R_1 X is a D-amino acid ^{residue}



20570X

wherein R is

5 (a) a carbocyclic aryl-containing radical selected from the group consisting of naphthyl, anthryl, fluorenyl, phenanthryl, biphenyl, benzhydryl and phenyl substituted with three or more straight chain lower alkyl groups; or

10 (b) a saturated carbocyclic radical selected from the group consisting of cyclohexyl substituted with three or more straight chain lower alkyl groups, perhydro-naphthyl, perhydrobiphenyl, perhydro-2,2-diphenylmethyl and adamantyl;

15 Y is leucyl, isoleucyl, nor-leucyl or N-methyl-leucyl;

Z is glycnamide or $-\text{NH}-\text{R}^1$, wherein

R¹ is lower alkyl, cycloalkyl, fluoro lower alkyl or

20 ~~20571X~~ $-\text{NH}-\text{C}(=\text{O})-\text{NH}-\text{R}^2$ wherein

R² is hydrogen or lower alkyl, or a pharmaceutical composition containing same.

25 16. A pharmaceutical composition for treatment of benign prostatic hypertrophy in a male mammal comprising a compound of the formula

(pyro)Glu-His-V-Ser-W-X-Y-Arg-Pro-Z

(I)

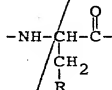
30

or a pharmaceutically acceptable salt thereof wherein:

V is tryptophyl, phenylalanyl or 3-(1-naphthyl)-L-alanyl;

W is tyrosyl, phenylalanyl or 3-(1-pentafluorophenyl)-L-alanyl;

X is a D-amino acid



wherein R is

(a) a carbocyclic aryl-containing radical selected from the group consisting of naphthyl, anthryl, fluorenyl, phenanthryl, biphenyl, benzhydryl and phenyl substituted with three or more straight chain lower alkyl groups; or

(b) a saturated carbocyclic radical selected from the group consisting of cyclohexyl substituted with three or more straight chain lower alkyl groups, perhydro-naphthyl, perhydrobiphenyl, perhydro-2,2-diphenylmethyl and adamantyl;

Y is leucyl, isoleucyl, nor-leucyl or N-methyl-leucyl;

Z is glycine or -NH-R¹, wherein

R¹ is lower alkyl, cycloalkyl, fluoro lower alkyl or
 -NH-C(=O)-NH-R^2 wherein

R² is hydrogen or lower alkyl, in admixture with a pharmaceutically acceptable, non-toxic carrier.

15.
17. A method of inhibiting spermatogenesis in a male mammalian subject which method comprises

administering to said subject an effective amount of a compound of the formula P_5

71 (pyro)Glu-His-V-Ser-W-X-Y-Arg-Pro-Z 71(1) P5

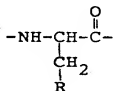
(I)

P_5 or a pharmaceutically acceptable salt thereof wherein:

P_1 V is tryptophyl, phenylalanyl or 3-(1-naphthyl)-L-alanyl;

P_1 W is tyrosyl, phenylalanyl or 3-(1-pentafluorophenyl)-L-alanyl;

P_1 X is a D-amino acid ^{residue}



70590X

$P_1 = 10$ wherein R is

P_2 (a) a carbocyclic aryl-containing radical selected from the group consisting of naphthyl, anthryl, fluorenyl, phenanthryl, biphenyl, benzhydryl and phenyl substituted with three or more straight chain lower alkyl groups; or

P_2 (b) a saturated carbocyclic radical selected from the group consisting of cyclohexyl substituted with three or more straight chain lower alkyl groups, perhydro-naphthyl, perhydrobiphenyl, perhydro-2,2-diphenylmethyl and adamantyl;

P_1 Y is leucyl, isoleucyl, nor-leucyl or N-methyl-leucyl;

P_1 Z is glycnamide or $\frac{1}{N_1}\text{-NH-R}^1$, wherein

TOGGY R^1 is lower alkyl, cycloalkyl, fluoro lower alkyl or
 $-NH-\overset{\overset{O}{\parallel}}{C}-NH-R^2$ wherein

R^2 is hydrogen or lower alkyl, or a pharmaceutical composition containing same.

18. A pharmaceutical composition for inhibiting spermatogenesis in a male mammal comprising a compound of the formula

(pyro)Glu-His-V-Ser-W-X-Y-Arg-Pro-Z

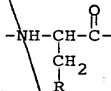
(I)

and the pharmaceutically acceptable salts thereof wherein:

V is tryptophyl, phenylalanyl or 3-(1-naphthyl)-L-alanyl;

W is tyrosyl, phenylalanyl or 3-(1-pentafluorophenyl)-L-alanyl;

X is a D-amino acid



wherein R is

(a) a carbocyclic aryl-containing radical selected from the group consisting of naphthyl, anthryl, fluorenyl, phenanthryl, biphenyl, benzhydryl and phenyl substituted with three or more straight chain lower alkyl groups; or

(b) a saturated carbocyclic radical selected from the group consisting of cyclohexyl substituted with three or more straight chain lower alkyl groups, perhydro-

naphthyl, perhydrobiphenyl, perhydro-2,2-diphenylmethyl and adamantyl;

Y is leucyl, isoleucyl, nor-leucyl or N-methyl-leucyl;

Z is glycnamide or -NH-R^1 , wherein

R^1 is lower alkyl, cycloalkyl, fluoro lower alkyl or -NH-C(=O)-NH-R^2 wherein

R^2 is hydrogen or lower alkyl, in admixture with a pharmaceutically acceptable, non-toxic carrier.

19. A process for the preparation of a compound of the formula

(pyro)Glu-His-V-Ser-W-X-Y-Arg-Pro-Z

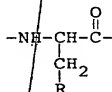
(I)

and the pharmaceutically acceptable salts thereof wherein:

V is tryptophyl, phenylalanyl or 3-(1-naphthyl)-L-alanyl;

W is tyrosyl, phenylalanyl or 3-(1-pentafluorophenyl)-L-alanyl;

X is a D-amino acid



wherein R is

(a) a carbocyclic aryl-containing radical selected from the group consisting of naphthyl, anthryl, fluorenyl, phenanthryl, biphenyl, benzhydryl and phenyl

substituted with three or more straight chain lower alkyl groups; or

(b) a saturated carbocyclic radical selected from the group consisting of cyclohexyl substituted with three or more straight chain lower alkyl groups, perhydronaphthyl, perhydrobiphenyl, perhydro-2,2-diphenylmethyl and adamantyl;

Y is leucyl, isoleucyl, nor-leucyl or N-methyl-leucyl;

Z is glycinamide or -NH-R^1 , wherein

R^1 is lower alkyl, cycloalkyl, fluoro lower alkyl or -NH-C(=O)-NH-R^2 wherein

R^2 is hydrogen or lower alkyl, which process comprises:

(i) removing protecting groups and optionally covalently bound solid support from a protected polypeptide to afford a compound of Formula (I) or a salt thereof, and optionally

(ii) converting a compound of Formula (I) to a pharmaceutically acceptable salt,

(iii) converting a salt of a compound of Formula (I) to a pharmaceutically acceptable salt, or

(iv) decomposing a salt of a compound of Formula (I) to a free polypeptide of Formula (I).